PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC32050A	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IB2005/000016	International filing date *(day/month/year)* 03.01.2005	Priority date *(day/month/year)* 13.01.2004
International Patent Classification (IPC) or national classification and IPC C07D295/08, A61K31/495		
Applicant PFIZER LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.01.2005	18.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Usuelli, A Telephone No. +49 89 2399-7366

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2005/000016

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-61 as originally filed

   Claims, Numbers

   1-22 received on 05.07.2005 with letter of 30.06.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1 (part)-10(part), 12(part)-22(part)

because:

☒ the said international application, or the said claims Nos. 18-21 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1 (part)-10(part), 12(part)-22(part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17,22
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of the compounds of formula (I). So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Art. 6 PCT). For these reasons, it has not been possible to carry out a meaningful search over the whole breadth of the claims. Consequently, the search has been restricted to the parts of the claims concerning the compounds of formula (I) wherein R2 is as defined in claim 3 and R3 is as defined in claim 6 (i.e. the compounds of the part of claim 6 depending from claim 3)

The preliminary examination will concern the parts of the claims for which a complete search has been carried out. (Rule 66.1 PCT)

2- Claims 18-21 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents:

d1: JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. vol. 30, 30 March 1987, pages 1779-1787

d2: JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1998, pages 2243-2246

d3: US-A-4 162 316

d4: JOURNAL OF MEDICINAL CHEMISTRY, vol. 22, no. 1, 1979, pages 58-63

d5: JOURNAL OF MEDICINAL CHEMISTRY, vol. 18, no. 12, 1975, pages 1240-

1244,

d6: DATABASE CROSSFIRE BEILSTEIN Database accession no. BRN: 561221

d7: US-A-5 561 152

d8: CNS DRUGS, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 4, no. 2, 1995, pages 79-89

2- Novelty

Present compounds of formula (I) are novel. Therefore, the requirements of Art. 33.2 PCT are met.

The compounds 19 and 20 of d1 and the compound disclosed at the end of Reference Example 7 in d3 are excluded by the scope of the claims for the effect of the proviso.
The products disclosed in Table 3 of d2 (entries 1 and 2), the general formula 7 of d4 and the compound of d6 differ from present compounds on account of the definition of present group A which is an unsubstituted methylene group.
The compound 4 of Scheme I of d5 is not novelty destroying in that the phenyl corresponding to present group R3 is unsubstituted.
D7 and d8 do not disclose any compound structurally close to the compounds of the invention.

3- Inventive step

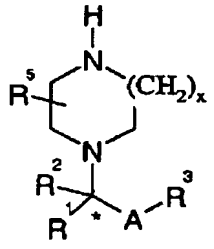
3.1-The applicant has set himself the task of providing compounds which exhibit activity as both serotonin and noradrenalin re-uptake inhibitors.
Documents d7 and d8 disclose compounds having the same use of present compounds.
Considering the chemical structures of the compounds disclosed in these documents, it is considered that d7 represents the closest state of the art.
The data disclosed in Table 1 of the present description provide the evidence that the compounds of formula (I) indeed possess the claimed activity.
Hence, the technical problem can be seen in the provision of further serotonin and noradrenalin re-uptake inhibitors.

3.2- Formula (I) of d7 includes also piperazine derivatives (cf. definition of R1 and R2). Present compound are structurally characterized by the presence of a chain (CH-A-) to which three rings are attached (the piperazine, R2 and R3). The compounds of d7 lack this

structural requirement.
The compounds disclosed in Fig. 1 of d8 appear to be structurally very different from present compounds.
Hence, the subject-matter of claims 1 to 22 is considered to comply with the requirements of Art. 33.3 PCT.

Claims:

1. A compound according to Formula I:



I

and pharmaceutically and/or veterinarily acceptable derivatives thereof, wherein:

R^1 is H;

R^2 is aryl, het, C_{3-8}cycloalkyl, C_{1-6}alkyl, $(CH_2)_z$aryl or R^4, wherein each of the cycloalkyl, aryl, het and R^4 groups is optionally substituted by at least one substituent independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, OH, halo, CF_3, OCF_3, $OCHF_2$, $O(CH_2)_yCF_3$, CN, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy, SCF_3, $C_{1-6}alkylSO_2$, C_{1-4}alkyl-S-C_{1-4}alkyl, C_{1-4}alkyl-S-, $C_{1-4}alkylNR^{10}R^{11}$ and $NR^{10}R^{11}$;

or R^1 and R^2, together with the carbon atom to which they are bound, form a 5- or 6-membered carbocyclic ring or a 5- or 6-membered heterocyclic ring containing at least one N, O or S heteroatom;

where R^1 and R^2 are different, * represents a chiral centre;

R^3 is aryl, het or R^4, each substituted by at least one substituent independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, het, OH, halo, CF_3, OCF_3, $OCHF_2$, $O(CH_2)_yCF_3$, CN, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy, SCF_3, $C_{1-6}alkylSO_2$, C_{1-4}alkyl-S-C_{1-4}alkyl, C_{1-4}alkyl-S-, $C_{1-4}alkylNR^{10}R^{11}$ and $NR^{10}R^{11}$;

R^4 is a phenyl group fused to a 5- or 6-membered carbocyclic group, or a phenyl group fused to a 5- or 6-membered heterocyclic group containing at least one N, O or S heteroatom;

R^5 is H or C_{1-6}alkyl;

R^{10} and R^{11} are the same or different and are independently H or C_{1-4}alkyl;

A is an unsubstituted methylene group;

x is an integer from 1 to 3;

y is 1 or 2;

z is an integer from 1 to 3;

aryl is phenyl, naphthyl, anthracyl or phenanthryl; and

het is an aromatic or non-aromatic 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 5- or 6-membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom,

provided that when R^1 is H, R^2 is phenyl, A is CH_2 and x is 1, R^3 is not 3-hydroxyphenyl or 3-(C_{1-4}alkoxy)phenyl.

2. A compound or a pharmaceutically acceptable salt thereof according to Claim 1, wherein R^1 is H.

3. A compound or a pharmaceutically acceptable salt thereof according to Claim 1 or Claim 2, wherein R^2 is aryl, het or C_{3-8}cycloalkyl, each optionally substituted by at least one substituent independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, OH, halo, CF_3, OCF_3, $OCHF_2$, $O(CH_2)_yCF_3$, CN, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy, SCF_3, $C_{1-6}alkylSO_2$ and C_{1-4}alkyl-S-C_{1-4}alkyl.

4. A compound or a pharmaceutically acceptable salt thereof according to Claim 3, wherein R^2 is aryl optionally substituted by at least one substituent independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, OH, halo, CF_3, OCF_3, $OCHF_2$, $O(CH_2)_yCF_3$, CN, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy, SCF_3, $C_{1-6}alkylSO_2$ and C_{1-4}alkyl-S-C_{1-4}alkyl.

5. A compound or a pharmaceutically acceptable salt thereof according to Claim 4, wherein R^2 is phenyl optionally substituted by at least one

substituent independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, OH, halo, CF_3, OCF_3, $OCHF_2$, $O(CH_2)_yCF_3$, CN, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy, SCF_3, $C_{1-6}alkylSO_2$ and C_{1-4}alkyl-S-C_{1-4}alkyl.

6. A compound or a pharmaceutically acceptable salt thereof according to any preceding claim, wherein R^3 is aryl or R^4, each substituted by at least one substituent independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, OH, halo, CF_3, OCF_3, $OCHF_2$, $O(CH_2)_yCF_3$, CN, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy, SCF_3, $C_{1-6}alkylSO_2$ and C_{1-4}alkyl-S-C_{1-4}alkyl.

7. A compound or a pharmaceutically acceptable salt thereof according to Claim 6, wherein R^3 is phenyl substituted by at least one substituent independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, OH, halo, CF_3, OCF_3, $OCHF_2$, $O(CH_2)_yCF_3$, CN, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy, SCF_3, $C_{1-6}alkylSO_2$ and C_{1-4}alkyl-S-C_{1-4}alkyl.

8. A compound or a pharmaceutically acceptable salt thereof according to any preceding claim, wherein R^5 is H or C_{1-6}alkyl.

9. A compound or a pharmaceutically acceptable salt thereof according to any preceding claim, wherein x is 1.

10. A compound or a pharmaceutically acceptable salt thereof according to Claim 1 which is (+) or (-)-1-[2-(2-Ethoxyphenyl)-1-phenylethyl]piperazine.

11. A compound or a pharmaceutically acceptable salt thereof according to Claim 1 which is selected from the group consisting of:

1-{1-Phenyl-2-[2-(trifluoromethoxy)phenyl]ethyl}piperazine;

1-{1-Phenyl-2-[2-chloro-6-fluorophenyl]ethyl}piperazine;

1-{1-Phenyl-2-[2-chlorophenyl]ethyl}piperazine;

1-{1-(3-Fluorophenyl)-2-[2-(trifluoromethoxy)phenyl]ethyl}piperazine;
1-{2-[2-(Difluoromethoxy)phenyl]-1-phenylethyl}piperazine;
1-{1-(4-Fluorophenyl)-2-[2-(trifluoromethoxy)phenyl]ethyl}piperazine;
1-{1-(2-Fluorophenyl)-2-[2-(trifluoromethoxy)phenyl]ethyl}piperazine; and
1-[2-(2-Methoxyphenyl)-1-phenylethyl]piperazine.

12. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as claimed in any one of Claims 1 to 11 and a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1-11 for use as a medicament.

14. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1-11 in the manufacture of a medicament for the treatment of a disorder in which the regulation of serotonin or noradrenaline in mammals is implicated.

15. Use according to Claim 14, wherein the regulation of serotonin and noradrenaline is implicated.

16. Use of a compound or a pharmaceutically acceptable salt thereof according to Claim 15 in the manufacture of a medicament for the treatment of urinary disorders, depression, pain, premature ejaculation, ADHD or fibromyalgia in mammals.

17. Use of a compound or a pharmaceutically acceptable salt thereof according to Claim 16, for the treatment of urinary incontinence, such as GSI or USI , in mammals.

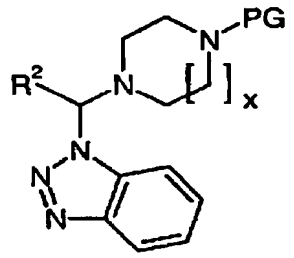
18. A method of treatment of a disorder in which the regulation of serotonin or noradrenaline is implicated which comprises administering a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1-11 to a patient in need of such treatment.

19. A method according to Claim 18, wherein the regulation of serotonin and noradrenaline is implicated.

20. A method of treatment of urinary disorders, depression, pain, premature ejaculation, ADHD or fibromyalgia, which comprises administering a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1-11 to a patient in need of such treatment.

21. A method according to Claim 20, wherein the urinary disorder is urinary incontinence, such as GSI or USI.

22. A process for preparing a compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1-11 comprising reacting a compound of Formula III



(III)

wherein R2 and x are as defined in any of Claims 1 to 11 and PG is a protecting group;

with a compound of Formula IV

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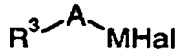

(IV)

wherein R3 and A are as defined in any of Claims 1 to 11, M is a metal selected from Zn and Mg and Hal is a halogen atom selected from chlorine, bromine and iodine;

and deprotecting the resultant compound.